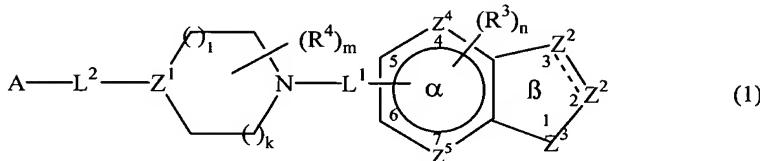


Claims

1. A compound of the formula:



and the pharmaceutically acceptable salts thereof, wherein

 represents a single or double bond;

each  $Z^2$  is independently  $CR^1$  or  $C(R^1)_2$  wherein each  $R^1$  is independently hydrogen or noninterfering substituent;

$Z^3$  is  $NR^7$ , O, or S;

$R^7$  is hydrogen or a non-interfering substituent;

each of  $Z^4$  and  $Z^5$  is independently N or  $CR^1$  wherein  $R^1$  is as defined above and wherein at least one of  $Z^4$  and  $Z^5$  is N;

each  $R^3$  is independently a noninterfering substituent;

$n$  is 0-3;

each of  $L^1$  and  $L^2$  is a linker;

each  $R^4$  is independently a noninterfering substituent;

$m$  is 0-4;

$Z^1$  is  $CR^5$  or N wherein  $R^5$  is hydrogen or a noninterfering substituent;

each of  $l$  and  $k$  is an integer from 0-2 wherein the sum of  $l$  and  $k$  is 0-3;

$A$  is a cyclic group substituted with 0-5 noninterfering substituents, wherein two said noninterfering substituents can form a fused ring.

2. The compound of claim 1 wherein one  $R^1$  is  $-W_i-COX_jY$  wherein  $Y$  is  $COR^2$  or an isostere thereof and  $R^2$  is hydrogen or a noninterfering substituent, each of  $W$  and  $X$  is a spacer of 2-6 Å, and each of  $i$  and  $j$  is independently 0 or 1.

3. The compound of claim 2 wherein said R<sup>1</sup> is COX<sub>j</sub>COR<sup>2</sup> and wherein R<sup>2</sup> is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, OR, NR<sub>2</sub>, OCOR, NRCOR, NRCONR<sub>2</sub>, NRSO<sub>2</sub>R, NRSO<sub>2</sub>NR<sub>2</sub>, OCONR<sub>2</sub>, CN, COOR, CONR<sub>2</sub>, COR, or R<sub>3</sub>Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R<sup>2</sup> is OR, NR<sub>2</sub>, SR, NRCONR<sub>2</sub>, OCONR<sub>2</sub>, or NRSO<sub>2</sub>NR<sub>2</sub>, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR<sub>2</sub>, OCOR, NRCOR, NRCONR<sub>2</sub>, NRSO<sub>2</sub>R, NRSO<sub>2</sub>NR<sub>2</sub>, OCONR<sub>2</sub>, or R<sub>3</sub>Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is alkylene.

4. The compound of claim 3 wherein j is 0.

5. The compound of claim 1 wherein R<sup>7</sup> is H or is optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO<sub>2</sub>R, RCO, COOR, alkyl-COR, SO<sub>3</sub>R, CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, NR<sub>2</sub>, OR, alkyl-SR, alkyl-SOR, alkyl-SO<sub>2</sub>R, alkyl-OCOR, alkyl-COOR, alkyl-CN, alkyl-CONR<sub>2</sub>, or R<sub>3</sub>Si, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

6. The compound of claim 5 wherein R<sup>7</sup> is H, or is optionally substituted alkyl, optionally substituted acyl, OR, or NR<sub>2</sub> wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

7. The compound of claim 1 wherein both k and l are 1.

8. The compound of claim 1 wherein L<sup>1</sup> is CO, CHO or CH<sub>2</sub>.

9. The compound of claim 8 wherein L<sup>1</sup> is CO.

10. The compound of claim 1 wherein Z<sup>1</sup> is N.

11. The compound of claim 1 wherein Z<sup>1</sup> is CR<sup>5</sup> wherein R<sup>5</sup> is H, OR, NR<sub>2</sub>, SR or halo, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof,

12. The compound of claim 1 wherein L<sup>2</sup> is alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR<sub>2</sub>, SR, SOR, SO<sub>2</sub>R, OCOR, NRCOR, NRCONR<sub>2</sub>, NRCOOR, OCONR<sub>2</sub>, RCO, COOR, alkyl-OOR, SO<sub>3</sub>R, CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, NRSO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, R<sub>3</sub>Si, and NO<sub>2</sub>, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L<sup>2</sup> can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

13. The compound of claim 12 wherein L<sup>2</sup> is unsubstituted alkylene.

14. The compound of claim 13 wherein L<sup>2</sup> is unsubstituted methylene.

15. The compound of claim 1 wherein A is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR<sub>2</sub>, SR, SOR, SO<sub>2</sub>R, OCOR, NRCOR, NRCONR<sub>2</sub>, NRCOOR, OCONR<sub>2</sub>, RCO, COOR, alkyl-OOR, SO<sub>3</sub>R, CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, NRSO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, R<sub>3</sub>Si, and NO<sub>2</sub>, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

16. The compound of claim 15 wherein A is optionally substituted phenyl.

17. The compound of claim 16 wherein said optional substitution is by halo, OR, or alkyl.
18. The compound of claim 17 wherein said phenyl is unsubstituted or has a single substituent.
19. The compound of claim 1 wherein  $R^4$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-royl, halo, OR, NR<sub>2</sub>, SR, SOR, SO<sub>2</sub>R, OCOR, NRCOR, NRCNR<sub>2</sub>, NRCOOR, OCONR<sub>2</sub>, RCO, COOR, alkyl-OOR, SO<sub>3</sub>R, CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, NRSO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, R<sub>3</sub>Si, and NO<sub>2</sub>, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of  $R^4$  on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or  $R^4$  is =O or an oxime, oximeether, oximeester or ketal thereof.
20. The compound of claim 19 wherein each  $R^4$  is halo, OR, or alkyl.
21. The compound of claim 20 wherein m is 0, 1, or 2.
22. The compound of claim 21 wherein m is 2 and both  $R^4$  are alkyl.
23. The compound of claim 1 wherein each  $R^3$  is halo, alkyl, heteroalkyl, OCOR, OR, NRCOR, SR, or NR<sub>2</sub>, wherein R is H, alkyl, aryl, or heteroforms thereof.
24. The compound of claim 23 wherein  $R^3$  is halo or alkoxy.
25. The compound of claim 24 wherein n is 0, 1 or 2.
26. The compound of claim 1 wherein each  $R^1$  is independently hydrogen, or is alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-royl, halo, OR, NR<sub>2</sub>, SR, SOR, SO<sub>2</sub>R, OCOR, NRCOR, NRCNR<sub>2</sub>, NRCOOR, OCONR<sub>2</sub>, RCO, COOR, alkyl-OOR, SO<sub>3</sub>R, CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, NRSO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, R<sub>3</sub>Si, and NO<sub>2</sub>, wherein each R is independently H, alkyl, alkenyl or aryl

or heteroforms thereof and two of R<sup>1</sup> can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, and/or wherein one R<sup>1</sup> is optionally -W<sub>i</sub>-COX<sub>j</sub>Y wherein W, X, Y, i and j are as defined in claim 2.

27. The compound of claim 26 wherein one R<sup>1</sup> is -W<sub>i</sub>-COX<sub>j</sub>Y wherein W, X, Y, i and j are as defined in claim 2, and each other R<sup>1</sup> is selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR<sub>2</sub>, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

28. The compound of claim 1 wherein  represents a double bond.

29. The compound of claim 1 wherein Z<sup>4</sup> is N and Z<sup>5</sup> is CR<sup>1</sup>.

30. The compound of claim 1 wherein Z<sup>5</sup> is N and Z<sup>4</sup> is CR<sup>1</sup>.

31. The compound of claim 1 wherein both Z<sup>4</sup> and Z<sup>5</sup> are N.

32. The compound of claim 1 wherein the compound of formula (1) is selected from the group consisting of compounds made in Examples 1-53.

33. A pharmaceutical composition for treating conditions characterized by enhanced p38- $\alpha$  activity which composition comprises

a therapeutically effective amount of at least one compound of claim 1 and at least one pharmaceutically acceptable excipient.

34. The composition of claim 33 which further contains an additional therapeutic agent.

35. The composition of claim 34 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

36. A method to treat a condition mediated by p38 kinase comprising administering to a subject in need of such treatment a compound of claim 1, or a pharmaceutical composition thereof.
37. The method of claim 36 wherein said condition is a proinflammation response.
38. The method of claim 37 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease, cystic fibrosis, silicosis, pulmonary sarcosis, bone fracture healing, a bone resorption disease, soft tissue damage, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, Alzheimer's disease or pyresis.
39. The compound of claim 1 wherein the compound of formula (1) is selected from the group consisting of compounds made in Examples 1-27.
40. The compound of claim 1 wherein the compound of formula (1) is selected from the group consisting of compounds made in Examples 28-53.
41. The compound of claim 1 wherein the compound of formula (1) is selected from the group consisting of compounds made in Examples 7, 8, 11-27, and 33-47.